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09/870,414	05/30/2001	Anton-Lewis Usala	35626/234825	7087

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EXAMINER	
GUPTA, ANISH	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/870,414	USALA, ANTON-LEWIS	
	Examiner	Art Unit	
	ANISH GUPTA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date. _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants Brief filed, 6-30-06, is acknowledged. Due to the addition of the reference Mansbridge, the finality is hereby withdrawn and new grounds for rejection (incorporating the disclosure of Mansbridge) have been applied.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

2. Claims 1-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Usala (WO00/02999) in view of Miller et al. and Mansbridge et al. in further view of Davis or Pickart et al. remain rejected for the reason set forth in the previous office action under Usala in view of Miller and the reasons set forth below.

The reference of Usala teaches a composition that is useful in the stimulation of vascularization at a site in a mammal for wound healing. The composition disclosed contains L-glutamic acid at a concentration of betxveen 2-60mN, L-lysine at a concentration of .5 to 30raM, Arginine at a concentration of 1 to 40mM, Gelatin at a concentration of .01 to 40 raM, L-cysteine at a concentration of 5 to 500 gM, aminoguanidine at a concentration of 5 to bt500, intact collage at a concentration of() to 5 raM, EDTA at a concentration of 0 to 10raM, and dextran at a concentration of() to 2mM (see page 22, table 3). The gelatin in the composition is denatured collagen (see page 19, line 11). Note that this composition encompasses all of the limitations of all of the claims for the composition and concentration of the agent used, including the most inclusive claim 48 of the instant application. The reference states that the matrix is the ability to stimulate or enhance vascularization in surrounding tissue (see page 16, lines 13-14). The reference states that "the matrix may be used to treat conditions benefited by increased vascularization" (see page 16, lines 24-25). The reference further states that the mode of administration includes injection of the matrix directly onto the site (see page 18, lines 22-24), thereby meeting the limitation of claims 45 and 49. The reference also exemplifies preparations wherein 15mL of the matrix is used in the preparation and examples wherein the subject was injected with 8cc of the matrix (see page 23, lines 25-27 and page 26, example 6), thereby meeting the limitations of claims 30 and 50. The difference between the prior art and the instant application is that the reference does not disclose treatment of diabetic foot ulcers.

However, Miller teach that therapy for the treatment of diabetic foot ulcers includes vascular repair of the ulcers (see abstract). Miller et al. states that an ulcer gores through granulation and reepithelialization (see page 761). Further, the reference suggest that numerous agents can be administered to the to the ulcer site to provide an optimal environment for healing. These include

antibiotics and growth factors that result in the stimulation of granulation of tissue (see page 762, paragraph bridging column 1 an d2). It is well known in the art that granulation of tissue consists of new blood vessel formation, fibroblast activity, and re-epitelialization (see col., lines 29-35 of Davis US 5487899 and Col. 1, lines 28-35 of Pickart et al. US 5059588). Mansbridge also teaches that the angiogenesis (i.e. vascularization) is a goal for treating diabetic foot ulcers. This reference disclose that a goal of treatment for chronic diabetic foot ulcers is to redirect to an acute course and to reinstate normal wound healing. "This requires angiogenesis to improve the blood supply, and provision of suitable substratum for re-reepithelialization." (see page 404). The reference specifically discloses the mechanism of healing diabetic foot ulcers involves multiple components acting in concert, which include angiogenesis and promotion of re-reepithelialization (see page 413). The reference specifically demonstrates the beneficial effects of an angiogenic agent in the treatment of diabetic foot ulcers. The reference specifically points to angiogenesis as one of the mechanism by which this agent exerts the benefit (see page 412-413) Thus, since the US patent teaches method of treating disorders revascularization and since the art recognizes that revascularatization, a component of angiogenesis, is important in the healing diabetic foot ulcers, it would have been obvious to use the claimed composition for the treatment of foot ulcers because therapy for diabetic foot ulcers include vascular repair of the tissue.

3. Claims 1-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Usala (US 6231881) in view of Miller et al. and Mansbridge et al. in further view of Davis or Pickart et al. for the reason set forth in the previous office action under and the reasons set forth below.

The reference teaches a composition that is useful in the stimulation of vascularization at a site in a mammal for wound healing. The composition disclosed contains L-glutamic acid at a

concentration of between 2-60raN,],-lysine at a concentration of .5 to 30mM, Arginine at a concentration of 1 to 40raM, Gelatin at a concentration of .01 to 40 raM, L-cysteine at a concentration of 5 to 500 laM, aminoguanidine at a concentration of 5 to btS00, intact collage at a concentration of 0 to 5 mM, EDTA at a concentration of 0 to 10mM, and dextran at a concentration of 0 to 2mM (see col. 12, table 3). The gelatin in the composition is denatured collagen (see col. 12, lines 39-40). Note that this composition encompasses all of the limitations of all of the claims for the composition and concentration of the agent used, including the most inclusive claim 48 of the instant application. The reference states that the matrix is the ability to stimulate or enhance vascularization in surrounding tissue (see col. 8, lines 60-67). The reference states that "the matrix may be used to treat conditions benefited by increased vascularization" (see col. 9, lines 10-11). The reference further states that the mode of administration includes injection of the matrix directly onto the site (see col. 8, lines 25-30), thereby meeting the limitation of claims 45 and 49. 'lhe reference "also exemplifies preparations wherein 15ml, of the matrix is used in the preparauou axld examples wherein tile subject was injected with 8cc of the matrix (see col. 13, lines 4-6 and col. 14, ex~unple 6), thereby meeting the limitations of claims 30 and 50. The difference between the prior art and the instant application is that the reference does not disclose treatment of diabetic foot ulcers.

However, Miller teach that therapy for the treatment of diabetic foot ulcers includes vascular repair of the ulcers (see abstract). Miller et al. states that an ulcer gores through granulation and reepithelialization (see page 761). Further, the reference suggest that numerous agents can be administered to the to the ulcer site to provide an optimal environment for healing. These include antibiotics and growth factors that result in the stimulation of granulation of tissue (see page 762, paragraph bridging column 1 an d2). It is well known in the art that granulation of tissue consists of

new blood vessel formation, fibroblast activity, and re-epitelialization (see col., lines 29-35 of Davis US 5487899 and Col. 1, lines 28-35 of Pickart et al. US 5059588). Mansbridge also teaches that the angiogenesis (i.e. vascularization) is a goal for treating diabetic foot ulcers. This reference disclose that a goal of treatment for chronic diabetic foot ulcers is to redirect to an acute course and to reinstate normal wound healing. "This requires angiogenesis to improve the blood supply, and provision of suitable substratum for re-reepithelialization." (see page 404). The reference specifically discloses the mechanism of healing diabetic foot ulcers involves multiple components acting in concert, which include angiogenesis and promotion of re-reepithelialization (see page 413). The reference specifically demonstrates the beneficial effects of an angiogenic agent in the treatment of diabetic foot ulcers. The reference specifically points to angiogenesis as one of the mechanism by which this agent exerts the benefit (see page 412-413) Thus, since the US patent teaches method of treating disorders revascularization and since the art recognizes that revascularatization, a component of angiogenesis, is important in the healing diabetic foot ulcers, it would have been obvious to use the claimed composition for the treatment of foot ulcers because therapy for diabetic foot ulcers include vascular repair of the tissue.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 1-29-31-42, 46-48, and 50-51 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-57 of U.S. Patent No. 6,261,587 in view of Miller and in further view of Davis or Pickart et al.

5. The US patent claims a method of stimulating visualization at a site in a mammal by contacting the site with a matrix comprising denatured gelatin, dextran, nitric oxide inhibitor and a polar amino acid selected from Arginine, lysine, or glutamic acid (see claim 38). The gelatin is in the form of denatured collagen and is in the concentration range of between .01 to about 40mM of denatured collagen (see claim 44). Note that this concentration range is the same ranged claimed in claim 2 of the instant application. Further, the concentration of dextran is between 0 to about 2mM (claim 45) and polar amino acid between 3 to about 150 mM (claim 42). Both of the claimed concentration range is with the range claimed in claims 5, 8-9, and 33-36 of the instant application for dextran and the polar amino acids. Moreover, there is also the same concentration ranged claimed for the specific amino acids of glutamic, lysine and Arginine (see claim 43 of the US patent and claim 11-15 of the instant application. The nitric oxide inhibitors claimed in the US patent include dextran, heparin, cysteine, L-arginine, and aminoguanidine (see claims 21, 39-41 of the US patent). These nitric oxide inhibitors, including the concentration claimed in the US Patent, are similar to those claimed in claims 17-24 and 37-44 of the instant application. Note that claim 47 of the US patent claims a composition comprising dextran, denatured collagen, aminoguanidine, glutamic acid, lysine and arginine. This composition is similar to the composition claimed in claim 48 of the instant application. The difference between the US Patent and the claimed invention is that the US Patent does not teach the treatment of diabetic foot ulcers.

However, Miller teach that therapy for the treatment of diabetic foot ulcers includes vascular repair of the ulcers (see abstract). Miller et al. states that an ulcer gores through granulation and reepithelialization (see page 761). Further, the reference suggest that numerous agents can be administered to the to the ulcer site to provide an optimal environment for healing. These include antibiotics and growth factors that result in the stimulation of granulation of tissue (see page 762, paragraph bridging column 1 an d2). It is well known in the art that granulation of tissue consists of new blood vessel formation, fibroblast activity, and re-epitelialization (see col., lines 29-35 of Davis US 5487899 and Col. 1, lines 28-35 of Pickart et al. US 5059588). Mansbridge also teaches that the angiogenesis (i.e. vascularization) is a goal for treating diabetic foot ulcers. This reference disclose that a goal of treatment for chronic diabetic foot ulcers is to redirect to an acute course and to reinstate normal wound healing. "This requires angiogenesis to improve the blood supply, and provision of suitable substratum for re-reepithelialization." (see page 404). The reference specifically discloses the mechanism of healing diabetic foot ulcers involves multiple components acting in concert, which include angiogenesis and promotion of re-reepithelialization (see page 413). The reference specifically demonstrates the beneficial effects of an angiogenic agent in the treatment of diabetic foot ulcers. The reference specifically points to angiogenesis as one of the mechanism by which this agent exerts the benefit (see page 412-413) Thus, since the US patent teaches method of treating disorders revascularization and since the art recognizes that revascularatization, a component of angiogenesis, is important in the healing diabetic foot ulcers, it would have been obvious to use the claimed composition for the treatment of foot ulcers because therapy for diabetic foot ulcers include vascular repair of the tissue.

Response to Arguments to All of the Rejection

Applicants arguments have been addressed to the extent they read on the new rejection.

Applicants argue that the primary reference does not teach treatment of ulcerated tissue and lack any motivation for one of ordinary skill in the art to combine the references with Miller or vice versa. Applicants state that the treatment protocols recited in the Miller reference does not describe the treatment of diabetic foot ulcers by revascularization or angiogenesis. "Miller reference merely suggest that certain ulcers, specifically ischemic ulcer, vascular repair in the form of reconstructive vascular surgery is required to avoid amputation." The reference specifically discounts the suggestion that micorvascular disease is an etiologic factor and thus teaches away from the claimed invention. The single sentence relied upon in the reference regarding reepithelialization and granulation, does not provide motivation to use angiogenic agents. Rather, the only motivation provided is to utilize tissue debridement as a means for preparing an ulcer for granulation tissue and reepithelialization. The reference disclose the use of moist environment for reepithelialization, not antibiotics and growth factors. The reference is merely speculative with respect to benzoyl peroxide in the granulation of tissue.

Applicants assert that the rejections fail to credibly suggest that vascularization inducing agent would have a reasonable expectation of success as an ulcer treatment. Davis and Pickart only teach that blood vessel formation is one event that characterizes granulation of tissue. "There is nothing to suggest in either reference that encouraging of vascularization will lead to granulation of tissue. Applicants then assert that if the contention is correct, which Applicants does not admit, then one of ordinary skill in the art would view any vascularizing agent as beneficial treatment for ulcers. However, the state of the art is clearly inconsistent with this conclusion. Applicants make reference to the teachings of Levin and O'Neal's book which concludes "no clinical trials that have been proven FGF to be of benefit in clinical wound healing." Applicants also make reference to Richard et al. which concludes that FGF performed no better than placebo in reducing ulcer

perimeter and area. Based on the failures of FGF, the skilled artisan "would not expect each and every agent capable of triggering vascularization to automatically find success as n ulcer treatment."

Applicants arguments have been fully considered but have not been found persuasive.

The rejection has been supplemented with Mansbridge also teaches that the angiogenesis (i.e. vascularization) is a goal for treating diabetic foot ulcers. This reference disclose that a goal of treatment for chronic diabetic foot ulcers is to redirect to an acute course and to reinstate normal wound healing. "This requires angiogenesis to improve the blood supply, and provision of suitable substratum for re-reepithelialization." (see page 404). The reference specifically discloses the mechanism of healing diabetic foot ulcers involves multiple components acting in concert, which include angiogenesis and promotion of re-reepithelialization (see page 413). The reference specifically demonstrates the beneficial effects of an angiogenic agent in the treatment of diabetic foot ulcers. The reference specifically points to angiogenesis as one of the mechanism by which this agent exerts the benefit (see page 412-413). Thus, one of ordinary skill in the art would be motivated in using a agent that exerts vascularization, i.e. angiogenesis.

With respect to the statements regarding vascularization will lead to granulation of tissue, such conclusions are respectfully disagreed. It is well known in the art Angiogenesis, which forms granulation tissue, is the process by which a new microcirculation is built to support the healing wound. The new blood vessels become clinically visible within the wound space by four days after injury. Vascular endothelial cells, fibroblasts, and smooth muscle cells all proliferate in coordination to support wound granulation.

Simultaneously, re-epithelialization occurs to reestablish the epithelial cover. Epithelial cells from the wound margin or from deep hair follicles migrate across the wound and establish themselves over the granulation tissue and provisional matrix. Growth factors such as keratinocyte

growth factor (KGF) mediate this process. Several models (sliding versus rolling cells) of epithelialization exist.

Finally, with respect to the art cited by Applicants, the reference of Levin disclose numerous growth factors and yet Applicants focus only one a single growth factor to conclude, seemingly, that none would be expected to work. The rejection now sets forth a reference that disclose the use of growth factors that are effective in treating diabetic foot ulcers. Further, the secondary reference cited by Applicants concludes that "topical application of growth factors seems to be a logical means to promote wound repair in diabetic patients." (see page 67). Thus, one would, contrary to Applicants contentions, would be motivated to use factors that promote wound healing to treat ulcers. With respect to Richard, it does not conclusively state that bFGF is a complete failure. The reference states as bFGF, it might be locally de-graded and/or adsorbed into the dressing, losing part of its eventual efficacy. Indeed, it was recently reported that the concentration of bFGF, in the same formation were used, decreased by ~50% 4h after contact with sterile gauze. Thus, it is possible that incorporating bFGF into a gel or a cream might result in a significant effect."

Furthermore, in KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, ___, 82 USPQ2d 1385, 1397 (2007), the Supreme Court concluded that "obvious to try" may be an appropriate test under 103.

The Court stated in KSR When there is motivation

> "to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, ___, 82 USPQ2d 1385, 1397 (2007).

It would have been "obvious to try" to use a vascularization agent for the treament of diabetic foot ulcers because, the "problem" facing those in the art to goal for treatment of diabetic

foot ulcers is to redirect to an acute course and to reinstate normal wound healing. The art recognizes the use of vascularization/angiogenesis agent such as growth factors seems to be a logical means to promote wound repair in diabetic patients. The skilled artisan would have had reason to try to use vacularization agents to treat diabetic foot ulcers. Thus, "the product not of innovation but of ordinary skill and common sense," leading one to conclude that the product/process claimed is not patentable as it would have been obvious.

With respect to the claims that require specific locations of administering the gel of Usala, it would have been obvious to those treating ulcers the means and the locations to use the gel in the treatment of ulcers.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anish Gupta whose telephone number is (571)272-0965. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can normally be reached on (571) 272-0562. The fax phone number of this group is (571)-273-8300.

/Anish Gupta/
Primary Examiner, Art Unit 1654